Quantified Electroencephalographic Correlates of Depression in Alzheimer's Disease

Daniel Pozzi, Angel Golimstock, Ricardo Migliorelli, Alejandra Tesón, Horacio García, and Sergio Starkstein

While depression is one of the most frequent psychiatric problems among patients with probable Alzheimer's disease (AD), its mechanism is not well known. We performed quantified EEGs in a consecutive series of seven patients with mild dementia and depression, six patients with mild dementia and no depression, eight patients with moderate dementia and depression, and eight patients with moderate dementia and no depression. Regardless of the severity of dementia, depressed patients had a significantly higher percent theta in posterior brain areas. Moreover, depressed patients with mild AD showed a similar theta frequency as non-depressed patients with moderate AD. These findings suggest that the presence of depression may contribute to the qEEG changes of AD.

Key Words: Alzheimer's disease, depression, quantified electroencephalography

Introduction

Several studies have demonstrated significant differences in quantitative electroencephalographic (qEEG) activity between patients with Alzheimer's disease (AD) and normal elderly controls (Gordon et al 1968; Gerson et al 1976; Canter et al 1982; Coben et al 1983; Duffy et al 1984a; Penttila et al 1985; Visser et al 1985). In mild dementia, theta activity is increased and beta activity is decreased (Coben et al 1983 and 1985), while in more severe dementia alpha also decreases and delta activity increases (Stigsby et al 1981; Coben et al 1985; Penttila et al 1985).

Primary depression (i.e., depression in the absence of known brain lesions) is also related to significant qEEG changes. Decreases in delta and increases in alpha 1 power are observed when depressed elderly subjects are compared to non-depressed age-matched controls (Brenner et al 1986). However, other authors could not find differences between elderly depressed and non-depressed subjects (Visser et al 1985).

Depression is a common finding in AD, and about 50% of cross-sectional samples were reported to have (major or minor) depression (Loreck and Folstein 1993). While recent studies suggested the presence of biogenic amine changes among patients with AD and depression (Wolfe et al 1990), the mechanism of depression in AD is still unknown.

The main aim of the present study was to determine whether there are specific qEEG changes in depressed and non-depressed AD patients. We used a 2 × 2 design, with mood state (depressed or non-depressed) and severity of dementia (mild or moderate) as main factors.

From the Departments of Behavioral Neurology (DP, AG, RM, AT, SS) and Neurophysiology (DP, HG, SS), Raúl Carrea Institute of Neurological Research, Buenos Aires, Argentina.
Address reprint requests to Dr. Sergio Starkstein, Instituto de Investigaciones Neurológicas Raúl Carrea, Ayacucho 2166, Buenos Aires, Argentina.
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Patients and Methods

Patients

A consecutive series of patients with AD who attended the Neurology Clinic at our Institute at regular follow-up visits were screened for inclusion in our study. Patients were included if they met the National Institute of Neurological and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann et al 1984) and the Diagnostic and Statistical Manual for Mental Disorder, 3rd edition-revised (DSM-III-R) criteria for primary degenerative dementia of the Alzheimer's type (APA 1987). Patients underwent a standardized neurologic examination, laboratory testing, and CT scanning to exclude other causes of dementia. Patients were classified into different stages of dementia based on the Clinical Dementia Rating (CDR) and the DSM-III-R definitions for mild, moderate and severe dementia. The CDR is a global rating device which was found to distinguish unambiguously among older subjects with a wide range of cognitive function, from healthy to severely impaired (Hughes et al 1982). Patients with questionable or very mild dementia (CDR 0.5) and patients with severe dementia (CDR 3) were excluded. Thus, for the present study patients included in the mild dementia group were in the CDR 1 and met the DSM-III-R definition of mild dementia (i.e., although work or social activities are significantly impaired, the capacity for independent living remains, with adequate personal hygiene and relatively intact judgment), and patients in the moderate dementia group were in the CDR 2 and met the DSM-III-R definition of moderate dementia (i.e., independent living is hazardous, and some degree of supervision is necessary). Other exclusion criteria were 1) a focal lesion on the CT scan, and 2) a Hachinski Ischemic score > 4 (Hachinski et al 1975). Finally, patients on psychoactive drugs were withdrawn from the medications for at least 24 hr before the study.

Psychiatric and Neuropsychological Examination

All patients underwent a standardized psychiatric evaluation that included the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al 1990), which is a standardized psychiatric assessment that provides DSM-III-R–based diagnosis of psychiatric disorders. The SCID was assessed with the patient and at least two first-degree relatives. Based on these criteria, patients were classified as either depressed (major depression or dysthymia) or nondepressed. Severity of depression was measured with the Hamilton Depression Scale (HAM-D) (Hamilton 1967) using the patient as the source of information.

The Mini-Mental State Exam (MMSE) (Folstein et al 1975), an 11-item examination found to be valid and reliable in measuring cognitive deficits in AD, was used to measure global cognitive decline.

EEG Recording and Fourier Analysis

All EEG recordings were carried out by a trained neurologist using a 21-channel electroencephalograph (ATI MP24). Silver/silver chloride electrodes were applied to the scalp according to the international 10-20 system. The electrode positions were FP1, FP2, F7, F3, FZ, F4, F8, T3, C3, CZ, C4, T4, T3, P3, PZ, P4, T6, O1, OZ, and O2, with a linked-ears reference. After amplification, EEG data were passed through an antialiasing filter of 36 db per octave, and digitized at a sampling rate of 256 samples/sec per channel. The EEG samples were collected with both eyes closed and eyes open. Artifacts due to eye movement, muscle tension, and drowsiness were excluded after a visual inspection "off line" of the recording (i.e., the data were saved and used later to reject artifact-contaminated segments). A minimum of 30 epochs of one second of artifact-free EEG data were selected in each modality. A Fast Fourier Transformation was performed on each sample using a Hanning window (Blackman and Tukey 1958). The total range of analysis was 2–32 Hz and the EEG absolute power was calculated for the delta (2.0–3.9 Hz), theta (4.0–7.9 Hz), alpha$_1$ (8.0–10.9), alpha$_2$ (11.0–12.9), beta$_1$ (13.0–19.9), and beta$_2$ (20.0–32.0) frequencies.

Data Analysis

The following measures were computed: 1) Total power; 2) proportion (percent) of total power per frequency band (i.e., [band power/T] × 100, where T equals the sum of the power in all frequency bands from 2 to 32 Hz (Gerson et al 1976); 3) the alpha power/theta power ratio; and 4) reactivity of each band (i.e., eyes open/eyes closed).

To facilitate analysis of the topologic distribution of the total power, data were collapsed across electrodes into the following nine areas: A1 (F1-F3-F7); A2 (FZ-CZ); A3 (F2-F4-F8); A4 (T3-C3-T5); A5 (CZ-PZ); A6 (T4-C4-T6); A7 (P3-O1); A8 (PZ-OZ); and A9 (P4-02). Subsequently, percent band power was computed for each of these areas.

In order to fit the EEG data to a normal distribution, a log transformation of power data was calculated prior to statistical analysis. Statistical analysis involved one-way analysis of variance (ANOVA) and a multivariate analysis of variance (MANOVA). If significant main effects or interactions were found, a post-hoc analysis was carried out using the Tukey Honest significant difference (HSD) for equal samples, and the Tukey test for unequal samples (Spojotvoll & Stoline test).

Table 1. Demographic Findings

	DEP-MILD (N = 7)	DEP-MOD (N = 8)	NO-MILD (N = 6)	NO-MOD (N = 8)
Age (mean yrs)	71.4 (8.4)	74.0 (6.7)	74.5 (10.4)	71.1 (5.9)
Sex (% male)	29	25	66	50
Education (mean yrs)	9.7 (6.2)	7.2 (3.1)	11.2 (4.3)	13.0 (5.7)
Duration (mean yrs)	3.3 (1.5)	4.4 (3.2)	3.6 (1.6)	5.0 (4.2)
MMSE* (score)	22.5 (5.2)	12.6 (3.6)	22.6 (4.4)	17.1 (6.8)
HAM-D** (score)	14.5 (10.6)	18.5 (7.6)	1.3 (1.6)	5.6 (3.5)

*$F(3,25) = 6.06$, $p = 0.003$; post-hocs; Dep-mild *vs.* Dep-mod $p = 0.008$; Dep-mod *vs.* No-mild $p = 0.015$.
**$F(3,25) = 8.14$, $p = 0.0002$; post-hocs; Dep-mild *vs.* No-mild $p = 0.01$; Dep-mod *vs.* No-mod $p = 0.005$.
Means and standard deviations are in parentheses.

Table 2. Quantified Electroenecephalographic Findings

	DEP-MILD	DEP-MOD	NO-MILD	NO-MOD
Total Power (LN)	3.9 (0.2)	4.6 (0.5)	3.5 (0.3)	4.1 (0.6)
Delta (%)	13.4 (7.7)	12.4 (2.4)	11.2 (9.3)	9.5 (3.2)
Theta (%)	22.7 (10.1)	32.8 (12.8)	20.3 (3.0)	28.5 (12.8)
$Alpha_1$ (%)	25.5 (15.1)	20.7 (9.6)	40.4 (22.7)	24.2 (14.5)
$Alpha_2$ (%)	8.9 (2.5)	7.4 (2.4)	7.1 (5.2)	10.1 (5.9)
$Beta_1$ (%)	10.9 (4.3)	9.8 (3.8)	9.6 (5.0)	4.8 (10.2)
$Beta_2$ (%)	10.9 (4.3)	9.8 (3.8)	9.6 (5.0)	10.2 (4.8)
Alpha/theta (ratio)	1.4 (0.9)	0.9 (0.3)	2.2 (0.7)	1.4 (0.9)

Means and standard deviations in parentheses

Results

Patients were categorized according to the presence or absence of depression, and the severity of dementia (mild *vs.* moderate), into the following four groups: 1) mild dementia and depression (DEP-MILD) (n = 7), 2) moderate dementia and depression (DEP-MOD) (n = 8), 3) mild dementia and no depression (NO-MILD) (n = 6), and 4) moderate dementia and no depression (NO-MOD) (n = 8).

Demographic Findings (Table 1)

Our sample included 12 males (41.4%) and 17 females (58.6%) with a mean age (years ± SD) of 72.6 ± 7.5 (range: 54–85 years), and a mean duration of the disease (years ± SD) of 4.1 ± 3.4 years (range = 1–15 years). No significant between-group differences were found in any of the demographic variables.

Psychiatric Findings (Table 1)

As expected, depressed patients showed significantly higher HAM-D scores than non-depressed patients ($F(3,25) = 8.14$, $p = 0.0002$), but no significant severity of dementia by depression interaction for HAM-D scores was observed, indicating that the severity of depression was similar among patients with mild or moderate dementia. Moderately demented patients showed significantly lower MMSE scores than mildly demented patients ($F(3,25) = 6.06$, $p = 0.003$), but no dementia by depression interaction for MMSE scores was observed, revealing that the severity of cognitive impairments was similar between depressed and non-depressed patients (Table 1). Of the seven depressed patients with mild dementia, three had major depression and four had dysthymia. One of them had depressive episodes before the onset of AD, while the remaining six patients had depression after the onset of AD. The mean duration of depression for this group (weeks ± SD) was 35 ± 16. Of the eight depressed patients with moderate dementia, five had major depression and three had dysthymia. Four of them had depression before the onset of AD, while the remaining four patients had depression after the onset of AD. The mean duration of depression for this group (weeks ± SD) was 129.5 ± 117. Differences in the distribution of dysthymia and major depression, the onset of depression (i.e., before or after the onset of AD), and duration of depression between depressed patients with mild dementia and depressed patients with moderate dementia were not statistically significant ($\chi^2 = 0.06$, df = 1, p = NS, $\chi^2 = 0.83$, df = 1, p = NS, and $t = 1.88$, df = 6, p = NS, respectively).

Three non-depressed and four depressed patients were on small doses of benzodiazepines, and one non-depressed patient was on 25 mg of amitriptyline. While patients had received these medications for at least 3 months, drugs were withdrawn for at least 24 hrs before the study. No patient was on neuroleptics, and none of the remaining patients were on psychoactive drugs on a regular basis.

Neurophysiologic Findings (Table 2)

Due to eye movement artifacts, five eyes-open and one eyes-closed recordings had to be excluded.

TOTAL POWER. A 3-way (2-×-2-×-9) ANOVA with repeated measures was performed. Between-group factors

were depression (present or absent), severity of dementia (mild *vs.* moderate), and the nine regions identified above were the repeated factor. Significant main effects for both dementia severity and depression were noted. Total power was significantly greater in the moderately demented patients as compared to the mildly demented patients ($F(1,24) = 7.0$, $p = 0.014$), and depressed patients had significantly more total power than non-depressed patients ($F(1,24) = 4.4$, $p = 0.045$). The interaction effects were not significant.

RELATIVE POWER. A similar 3-way ANOVA with repeated measures was carried out for each band, but the region factor was collapsed into three regions: anterior (F1-F3-F7-FZ-CZ-F2-F4-F8), medial (T3-C3-T5-CZ-PZ-T4-C4-T6), and posterior (P3-01-PZ-OZ-P4-02). Analysis of the theta band showed a significant effect for dementia ($F(1,24) = 4.7$, $p = 0.039$). Patients with moderate dementia had a significantly higher theta power than mildly demented patients. There also was a significant depression-×-region interaction ($F(2,52) = 4.18$, $p = 0.02$). Patients with depression showed a significantly higher theta power in posterior regions than non-depressed patients. No significant main effects or interactions were found for the remaining five bands. Finally, we calculated a 3-way ANOVA using side (left, central, and right) as the repeated measure. There were no significant main effects or significant interactions for any of the six bands.

ALPHA/THETA RATIO. A 3-way ANOVA showed a significant main effect for dementia severity ($F(1,20) = 4.07$, $p < 0.05$). Patients with a moderate dementia showed a significantly lower alpha/theta ratio than patients with mild dementia. A significant main effect for depression was also found ($F(1,20) = 4.28$, $p < 0.05$). Depressed patients showed a significantly lower alpha/theta ratio than non-depressed patients (Figure 1). Finally, a significant depression by region interaction ($F(2,40) = 3.21$, $p < 0.05$) was the result of a significantly lower alpha/theta ratio in posterior areas in depressed as compared to non-depressed AD patients.

REACTIVITY. Reactivity ratios were analyzed using a 4-way ANOVA with repeated measures. Between-group factors were depression (present or absent), and severity of dementia (mild *vs.* moderate), and the two repeated factors were the nine areas and the six bands. There were no main effects or significant interactions.

Discussion

This is the first study to examine qEEG changes in depressed and non-depressed AD patients and showed several important findings. First, we have replicated previous

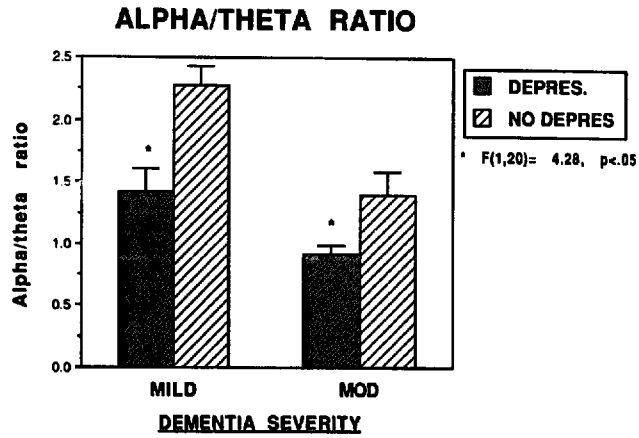

Figure 1. Bar graph showing mean values ± SE for the alpha/theta ratio for depressed and non-depressed patients with either mild or moderate dementia.

findings of increased theta power in more severely demented as compared to less demented AD patients. Second, we also found that depression significantly increased relative theta power in patients with AD. This finding was observed primarily in posterior brain areas. Third, the effect of depression on theta power was present in both mildly and moderately demented patients. Fourth, a decreased alpha/theta ratio was significantly related to both the severity of the dementia and the presence of depression. Fifth, while the decrease of the alpha/theta ratio associated with dementia was present in all brain areas, the alpha/theta ratio change associated with depression was restricted to posterior brain regions.

Before further discussion, some limitations of our study should be pointed out. First, due to the rather small sample, we collapsed patients with major and dysthymic depression in one group. Future studies should examine qEEG changes in major-depressed and dysthymic AD patients separately. Second, we did not include patients with severe dementia, and whether the present findings do also apply to severely demented AD patients with depression will need further studies. Finally, eight of our patients were on psychoactive medications. However, there were no significant between-group differences in the type of medications and dosages.

While depression has been frequently reported among AD patients, the neurobiologic correlates of mood change in AD have only recently been the focus of research. Zweig et al (1988) and Zubenko et al (1990) recently reported that depressed AD patients have significantly lower cell counts in the locus coeruleus and the substantia nigra as compared to non-depressed AD patients. Our finding of significant EEG changes in patients with AD and depression further supports the importance of biologic factors in the production of depression.

The question that now arises is whether the mechanism of depression in AD is similar to the mechanism of depres-

sion in patients with "primary" (i.e., no known brain injury) depression. Several studies using qEEG have examined patients with primary depression. Brenner et al reported that depressed patients had significantly less delta and more alpha$_1$ activity than controls, and significantly lower delta and theta and increased alpha$_2$ activity when compared to patients with dementia. However, they did not examine whether similiar findings were also present in demented patients with depression.

Our present findings among depressed AD patients are quite different. Depressed AD patients had a significantly higher theta relative power and a significantly lower alpha/theta ratio, and these changes were primarily observed in posterior brain regions (because there was an increase in posterior theta without a concomitant change in alpha, both relative theta power and the alpha/theta ratio may reflect the same phenomenon). While Brenner et al's and our present findings suggest different EEG correlates for primary depression and depression in AD, qEEG changes in primary depression have not been clearly established. Luthringer et al (1992) have recently reported significant increments in the theta relative power in depressed elderly patients as compared to age-matched controls, and a similar finding was noted in the present study. This issue will need further clarification in studies comparing depressed AD patients and age-matched patients with primary depression.

One additional important finding of the present study was that the qEEG changes produced by depression in AD were similar to qEEG changes produced by the severity of dementia. More severely demented patients (regardless of the presence of depression) and depressed AD patients (regardless of the severity of the dementia) both showed a significant decrease in the alpha/theta ratio. The only difference was that the depression-related qEEG changes were restricted to posterior brain area, whereas the dementia-related qEEG changes were observed over all brain areas.

Depression in AD is associated with a faster decline of intellectual functions and a significantly shorter survival (Pearson et al 1988; Rovner et al 1991). Our study demonstrates that in depressed and non-depressed patients with mild dementia and similar cognitive deficits, the qEEG changes of the depressed-mild dementia group resembled those found in non-depressed patients with moderate dementia. Thus, among depressed AD patients, qEEG changes were observed before further declines in intellectual functions and may constitute an important predictor for speed of cognitive decline.

In conclusion, the present study demonstrated a significant association between depression in AD and changes on qEEG, which are similar to those found in more severely demented patients. Whether these changes are a marker of a more aggressive progression of AD, and whether they are reversible upon treatment of the depression with antidepressant medication will be the focus of future studies.

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